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(54) Title: N-PHENYL-2-PYRIMIDINE-AMINE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to an N-phenyl-2-pyrimidine-amine derivative showing a superior effect on tumor, lung cancer, gastric cancer, etc. of warm-blooded animals and its salt. The present invention also relates to a process for preparing the compound and a pharmaceutical composition for the prevention and treatment of such diseases as tumor, lung cancer, gastric cancer, etc., which comprises the compound as an active ingredient.

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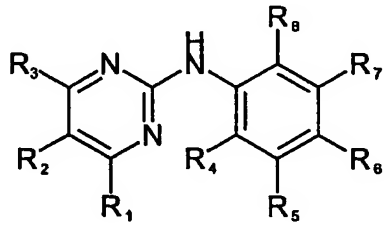
# N-PHENYL-2-PYRIMIDINE-AMINE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

## TECHNICAL FIELD

The present invention relates to a N-phenyl-2-pyrimidine-amine derivative represented by the following formula (1), which shows a superior effect on tumor, lung cancer, gastric cancer, etc. of warm-blooded animals:



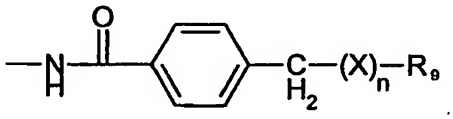
(1)

and its salt, in which

$R_1$ represents 3-pyridyl or 4-pyridyl,

$R_2$ and $R_3$ independently of one another represent hydrogen or lower alkyl,

$R_6$ or $R_7$ represents a radical having the following formula (2):



(2)

wherein X represents oxygen or NH, n=0 or 1, and $R_9$ represents aliphatic having at least 5 carbon atoms or heterocycle, or represents piperazinyl or homopiperazinyl each of which is substituted by lower alkyl, and

one or two among $R_4$, $R_5$, $R_7$, and $R_8$ when $R_6$ represents the radical of the above formula (2), or one or two among $R_4$, $R_5$, $R_6$, and $R_8$ when $R_7$ represents the radical of the above formula (2) independently of one another represent halogen, lower alkyl, or lower alkoxy, provided that $R_6$ or $R_7$ represents a radical of formula (2) wherein n=0 and $R_9$ is

4-methylpiperazine, then one or more of $R_4$, $R_5$, $R_7$, and $R_8$, or one or more of $R_4$, $R_5$, $R_6$, and $R_8$ are halogen.

The present invention also relates to a process for preparing the compound of formula (1) and a pharmaceutical composition for the prevention and treatment of such diseases as tumor, lung cancer, gastric cancer, etc., which comprises the compound of formula (1) or salt thereof as an active ingredient together with pharmaceutically acceptable carriers.

## BACKGROUND ART

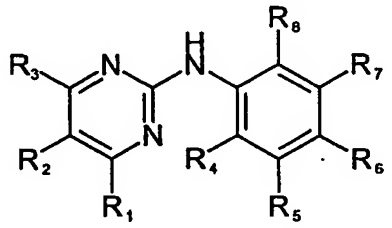
The earlier therapeutic agent for Chronic Myelogeous Leukemia (CML, below), Imatinib mesylate (Glivec, Korean Patent Laid-open Publication No. 1993-0021624 and Korean Patent Laid-open Publication No. 2001-0021950), has the structure of the above formula (1) wherein the amide type radical of formula (2) (n=0) is substituted at the position of $R_7$, $R_4$ is methyl, and $R_9$ is methylpiperazine, and so shows restrictive therapeutic effect, low stability, and several problems in its manufacturing process. That is, since Imatinib mesylate has a high hygroscopic property, it may be easily deteriorated under the influence of the ambient moisture. Therefore, this compound should be recrystallized from a specific solvent such as methanol in order to maintain a specific crystal form, and should be used soon after its preparation. Further, this compound exhibits a therapeutic effect only on the CML and little effect on the other sites, differently from other anti cancer agents. It is synthesized in the order that 4-chloromethylbenzoic acid is combined first with N-methylpiperazine, chlorination is carried out using thionyl chloride, and the resulting side moiety is combined with the basic structure, wherein the use of thionyl chloride causes many problems such as generation of toxic gas, explosion,

reduction of reaction yield, etc. Particularly, stability of the intermediate is not good to adversely affect the yield.

## DISCLOSURE OF THE INVENTION

Thus, the present inventors have extensively and intensively studied to improve the problems as stated above. As a result, the inventors have identified that the novel compound of formula (1) as defined above exhibits a superior effect, and then completed the present invention.

Therefore, a purpose of the present invention is to provide a N-phenyl-2-pyrimidine-amine derivative of the following formula (1):



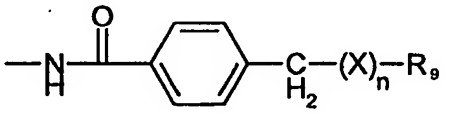
(1)

and its salt, in which

$R_1$ represents 3-pyridyl or 4-pyridyl,

$R_2$ and $R_3$ independently of one another represent hydrogen or lower alkyl,

$R_6$ or $R_7$ represents a radical having the following formula (2):



(2)

wherein X represents oxygen or NH, n=0 or 1, and $R_9$ represents aliphatic having at least 5 carbon atoms or heterocycle, or represents piperazinyl or homopiperazinyl each of which is substituted by lower alkyl, and

one or two among $R_4$, $R_5$, $R_7$, and $R_8$ when $R_6$ represents the radical of the above formula (2), or one or two among $R_4$, $R_5$, $R_6$, and $R_8$ when $R_7$ represents the radical of the above

formula (2) independently of one another represent halogen, lower alkyl, or lower alkoxy, provided that $R_6$ or $R_7$ represents a radical of formula (2) wherein n=0 and $R_9$ is 4-methylpiperazine, then one or more of $R_4$, $R_5$, $R_7$, and $R_8$, or one or more of $R_4$, $R_5$, $R_6$, and $R_8$ are halogen.

It is another purpose of the present invention to provide a process for preparing the compound of formula (1).

It is a further purpose of the present invention to provide a pharmaceutical composition for the prevention and treatment of such diseases as tumor, lung cancer, gastric cancer, etc., which comprises the compound of formula (1) or salt thereof as an active ingredient together with pharmaceutically acceptable carriers.

Below, the present invention will be explained in more detail.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the pharmacokinetic data of the compound of Example 4 according to the present invention compared with a standard drug of Imatinib mesylate.

## BEST MODE FOR CARRYING OUT THE INVENTION

In the above definitions for the substituents of N-phenyl-2-pyrimidine-amine derivative of formula (1), which shows a superior effect to tumor, lung cancer, gastric

cancer, etc. in warm-blooded animals, the term "lower alkyl" used alone or in a composite term with other terms preferably means straight-chain or branched and saturated aliphatic hydrocarbon radical having 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, isoamyl, n-hexyl, etc., but does not limited thereto.

The term "aliphatic having at least 5 carbon atoms" means alkenyl, alkynyl or alkyl having preferably carbon atoms of 22 or less, or more preferably carbon atoms of 10 or less.

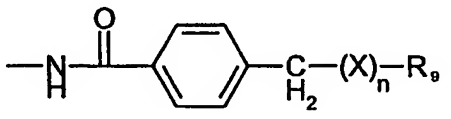
The term "heterocycle" means 5 to 7 membered saturated or unsaturated monocyclic radical, or means bi- or tri-cyclic radical optionally combined with benzene ring, each of which has 1 to 3 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur.

Preferable compounds among the compound of formula (1) showing a superior effect on tumor, lung cancer, gastric cancer, etc. include those wherein

$R_1$ represents 3-pyridyl,

$R_2$ and $R_3$ independently of one another represent hydrogen,

$R_6$ or $R_7$ represents a radical having the following formula (2):



(2)

wherein X represents NH, n=0 or 1, and $R_9$ represents piperidine, 4-methylhomopiperazine, or 4-methylpiperazine, and

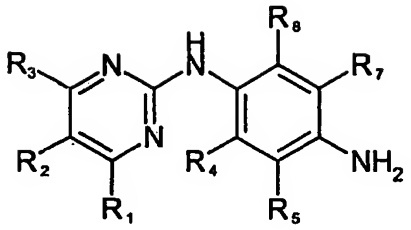
one or two among $R_4$, $R_5$, $R_7$, and $R_8$ when $R_6$ represents the radical of the above formula (2), or one or two among $R_4$, $R_5$, $R_6$, and $R_8$ when $R_7$ represents the radical of the above formula (2) independently of one another represent fluoro, methyl, or methoxy.

In the aspect of inhibition of protein kinase, particularly preferable compounds among the compound of formula (1) include those wherein $R_1$ represents 3-pyridyl, $R_2$, $R_3$, $R_4$, $R_5$, $R_7$, and $R_8$ independently of one another represent hydrogen, and $R_6$ represents the radical of formula (2) wherein n=0 and $R_9$ represents 4-methylhomopiperazine, or n=1, X represents NH, and $R_9$ represents 4-methylpiperazine.

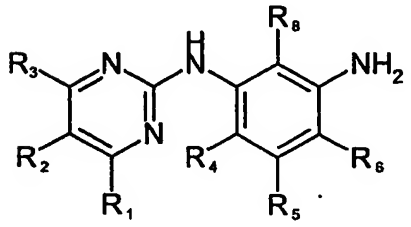
Further, the compound of formula (1) wherein $R_1$ represents 3-pyridyl, $R_2$ and $R_3$, independently of one another represent hydrogen, $R_4$ represents methyl, $R_5$, $R_6$ and $R_8$ independently of one another represent hydrogen, and $R_7$ represents the radical of formula (2) wherein n=1, X represents NH, and $R_9$ represents 4-methylpiperazine is particularly preferable.

The compound of formula (1) includes one or more basic groups or one or more basic radicals, and so may form an acid addition salt with aliphatic sulfonic acid (i.e., methanesulfonic acid, ethanesulfonic acid), hydrochloric acid, sulfuric acid, phosphoric acid, trifluoroacetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, citric acid, tartaric acid, oxalic acid, amino acid (i.e., lysine), benzoic acid, salicylic acid, etc. When several basic groups exist in a molecule, the compound of formula (1) may form mono or poly acid addition salt. Among the pharmaceutically acceptable salts as mentioned above, acetic acid salt and hydrochloric acid salt are better than methanesulfonic acid salt, since they have better solubility in water and show good absorptivity in Pk test.

According to the present invention, the compound of formula (1) as defined above and its salt can be prepared by a process which comprises reacting a compound represented by the following formula (3a) or (3b):

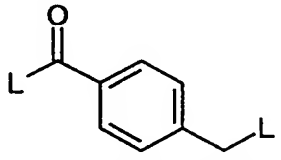


(3a)



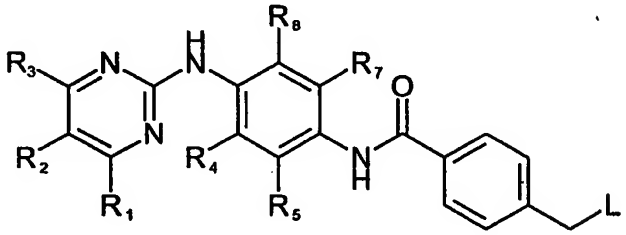
(3b)

wherein $R_1$ to $R_8$ are as defined above, with a compound represented by the following formula (4):

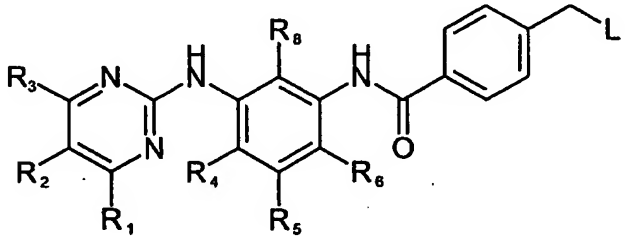


(4)

wherein L represents a leaving group, preferably halogen, to produce a compound represented by the following formula (5a) or (5b):



(5a)

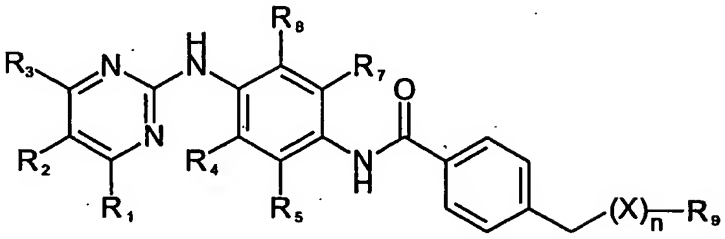


(5b)

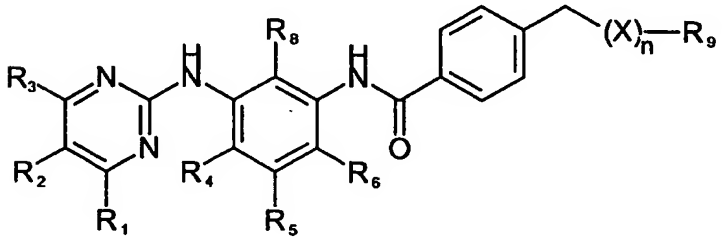
wherein $R_1$ to $R_8$ and L are as defined above, and reacting the compound of formula (5a) or (5b) with a compound represented by the following formula (6):

(6)

wherein X, n, and $R_9$ are as defined above, to give a compound represented by the following formula (1a) or (1b):



(1a)



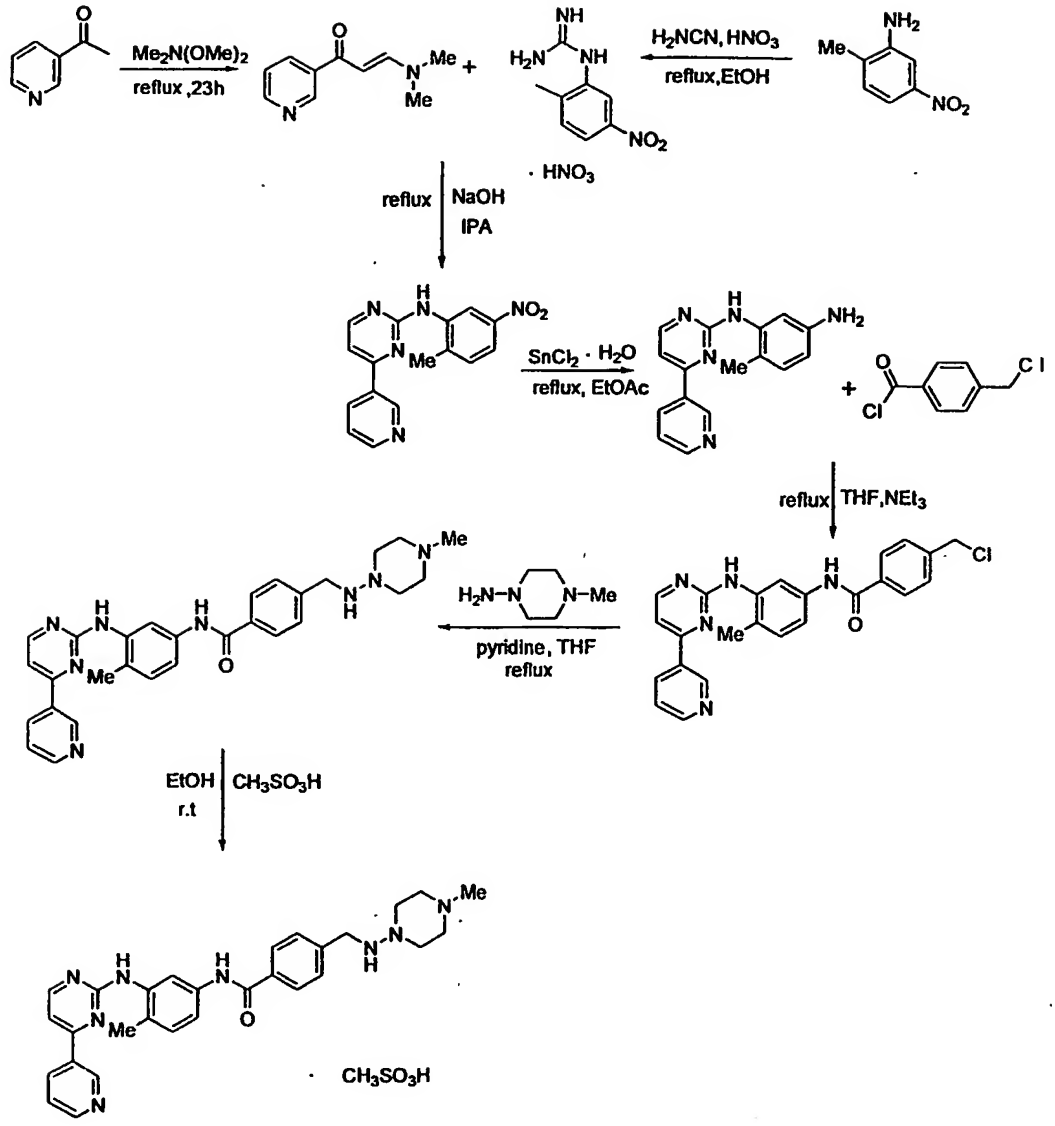
(1b)

wherein $R_1$ to $R_8$, X, n, and $R_9$ are as defined above. Therefore, it is another purpose of the present invention to provide the above process.

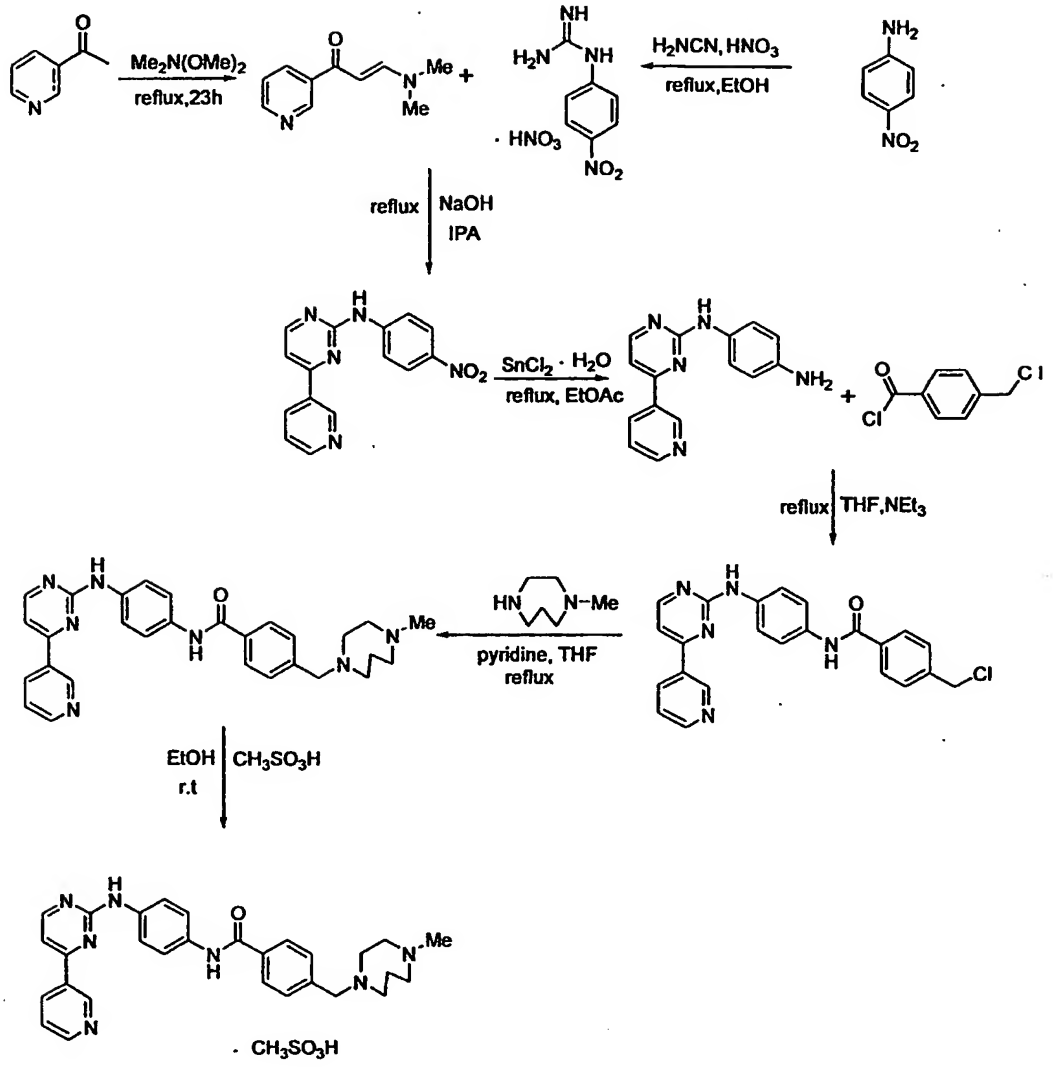
The above process according to the present invention is preferably carried out in a solvent and in the presence of a base. Any conventional solvent or base which does not adversely affect the reaction can be used, but one or more solvents selected from a group consisting of tetrahydrofuran, methylene chloride, ethanol, and methanol, and one or more bases selected from a group consisting of pyridine and triethylamine can be preferably mentioned.

Typical examples of the above process are depicted in the following Reaction Schemes 1 and 2. Any person skilled in the art can easily prepare the other compounds by referring to the specific examples.

Reaction Scheme 1



Reaction Scheme 2




The reaction may be conventionally carried out under cooling to warming. After the reaction is completed, the resulting product may be further purified by usual work-up processes, for example, column chromatography, recrystallization, etc.

The above process for preparing the compound of formula (1) of the present invention gives such advantages as stability of the chemical structure of the intermediates, simple control of reaction conditions, increase of the reaction yield, etc. when compared

with the known process comprising the steps of coupling the compound of formula (4) with the compound of formula (6) first, and then reacting the resulting compound with the compound of formula (3a) or (3b).

The compound of formula (1) of the present invention exhibits a superior effect on tumor, lung cancer, gastric cancer, etc., and so can be advantageously used for the prevention or treatment of those diseases. Particularly, the compound of formula (1) wherein X is NH shows better medicinal effect on CML than Imatinib mesylate, and the compound of formula (1) wherein the substituent of formula (2) is introduced into the position of $R_6$ shows an excellent anti-cancer activity on several parts of the body including lung, stomach, etc. Further, if the salt form of the compound of formula (1) is converted from methanesulfonate to acetate or hydro chloride, water solubility and absorptivity into the body of animals are highly increased. The effect of the compound of formula (1) and its salt according to the present invention can be confirmed by the test results of the following experiments.

When the active compound according to the present invention is used for clinical purpose, it is preferably administered in an amount ranging generally from 1 to 100㎎, preferably from 3 to 6㎎ per ㎏ of body weight a day. The total daily dosage may be administered once or over several times. However, the specific administration dosage for a patient can be varied with the specific compound used, body weight, sex or hygienic condition of the subject patient, diet, time or method of administration, excretion rate, mixing ratio of the agent, severity of the disease to be treated, etc.

The compound of the present invention may be administered in the form of injections or oral preparations.

Injections, for example, sterilized aqueous or oily suspension for injection, can be prepared according to the known procedure using suitable dispersing agent, wetting agent,

or suspending agent. Solvents which can be used for preparing injections include water, Ringer's fluid, and isotonic NaCl solution, and also sterilized fixing oil may be conveniently used as solvent or suspending media. Any non-stimulative fixing oil including mono- or di-glyceride may be used for this purpose. Fatty acid such as oleic acid may also be used for injections.

As the solid preparations for oral administration, capsules, tablets, pills, powders, granules, etc., preferably capsules and tablets can be mentioned. It is also desirable for tablets and pills to be formulated into enteric-coated preparations. The solid preparations may be prepared by mixing the active compound of formula (1) according to the present invention with at least one carrier selected from a group consisting of inactive diluents such as sucrose, lactose, starch, etc., lubricants such as magnesium stearate, disintegrating agent, and binding agent.

When the compound according to the present invention is clinically applied for the prevention and/or treatment of tumor, lung cancer, gastric cancer, etc., the active compound of formula (1) can be administered alone or in combination with the existing chemotherapeutic agents such as 5-Fu, cisplatin, taxol, methotrexate, anthracyclin, etc.

The present invention will be more specifically explained in the following Examples and Experiments. However, it should be understood that these Examples and Experiments are intended to illustrate the present invention but not in any manner to limit the scope of the present invention. In the following Examples, $R_f$ value was measured on silica gel (Merck, 60F254, Germany); the ratio of each solvent in the eluent mixture was volume ratio (v/v); and melting point was measured by DSC thermoanalysis instrument (NETZSCH, DSC204 cell). $^1$H-NMR was measured by Brucker, Ac-200.

## EXAMPLES

Preparation 1

N-(2-methyl-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (35g, 0.114mol) and stannous chloride dihydrate (128.5g, 0.569mol) were dissolved in a solvent mixture of ethyl acetate and ethanol (250㎖, 10/1, v/v), and the reaction solution was refluxed for 4 hours. The solution was cooled to room temperature, washed with 10% aqueous sodium hydroxide solution, and concentrated to give N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (35g).

$R_f$ = 0.45 (Methylene chloride : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.04(s,3H), 6.30-6.34(m,1H), 6.76-6.77(m,1H), 6.84-6.87 (d,1H), 7.34-7.35(m,1H), 7.50-7.56(m,1H), 8.38-8.47(m,1H), 8.53-8.57(m,2H), 8.66-8.70(m,1H), 9.23-9.24(d,1H)

The starting material was prepared as follows.

Step 1.1

3-Acetylpyridine (100g, 0.19mol) was added to dimethylformamide dimethylacetal (156.5g, 1.27mol), and the mixture was reacted under reflux for 23 hours. After the reaction mixture was cooled to 0°C, a mixture of diethyl ether and hexane (3:2, v/v) (500㎖) was added and the whole mixture was stirred for 4 hours. The resulting solid was filtered and washed with a mixture of diethyl ether and hexane(500㎖, 3/2, v/v) to give 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (120g).

$R_f$ = 0.46 (Methylene chloride : Methanol = 9 : 1)

$^1$H-NMR($CDCl_3$)= 3.04(s,3H), 3.24(s,3H), 5.83(s,1H), 5.89(s,1H), 7.48-7.55 (m,1H), 7.89-7.95(m,1H), 8.27-8.32(m,1H), 9.00-9.02(s,1H)

Step 1.2

2-Methyl-5-nitroaniline (100g, 0.657mol) was dissolved in ethanol (250㎖), and 65% aqueous nitric acid solution (48㎖, 0.65mol) was added thereto. When the exothermic reaction was stopped, cyanamide (41.4g) dissolved in water (41.4g) was added thereto. The brown mixture was reacted under reflux for 24 hours. The reaction mixture was cooled to 0°C, filtered, and washed with ethanol:diethyl ether(1:1, v/v) to give 2-methyl-5-nitrophenyl-guanidine nitrate (98g).

$R_f$ = 0.1 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.43(s,3H), 6.59(s,3H), 6.72-6.76(d,1H), 7.21-7.27(m,1H), 8.63-8.64(br,1H)

Step 1.3

3-Dimethylamino-1-(3-pyridyl)-2-propen-1-one (25g, 0.14mol), 2-methyl-5-nitrophenyl-guanidine nitrate (36g, 0.14mol), and sodium hydroxide (6.5g, 0.163mol) were dissolved in isopropanol and reacted under reflux for 18 hours. The reaction solution was cooled to 0°C, filtered, washed with isopropanol and methanol, and dried to give N-(2-methyl-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (20g).

$R_f$ = 0.6 (Methylene chloride : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.43(s,3H), 7.50-7.60(m,2H), 7.89-7.93(m,1H), 8.47-8.50 (m,1H), 8.62-8.64(m,1H), 8.71-8.74(m,1H), 8.78-8.81(m,1H), 9.27-9.33(m,2H)

Preparation 2

N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine(2.83g, 8.29mmol) was dissolved in tetrahydrofuran (20㎖), triethylamine (1.4㎖, 9.95mmol) was added thereto, and the mixture was stirred for 30 minutes. 4-Chloromethyl benzoyl chloride (2.03g, 10.78mmol) was added and the whole mixture was reacted under reflux for 4 hours.

The mixture was filtered, and the filtrate was concentrated and crystallized from water to give N-(5-(4-chloromethylbenzoylamino)-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (3.12g).

$R_f$ = 0.38 (Methylene chloride : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.23(s,3H), 4.45(s,2H), 7.20-7.24(d,1H), 7.43-7.61(m,5H), 7.94-7.98(d,1H), 8.09(s,1H), 8.50-8.53(d,1H), 9.02(s,1H), 9.28(s,1H), 10.27 (s,1H)

Example 1

N-(5-(4-chloromethylbenzoylamino)-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (1g, 2.33mmol) was dissolved in tetrahydrofuran (20㎖), pyridine (360㎕, 4.66mmol) was added thereto, and the mixture was stirred for 30 minutes. N-methylhomopiperazine (434㎕, 3.49mmol) was added thereto, and the mixture was refluxed for 12 hours and filtered. The filtrate was concentrated, subjected to column chromatography (eluent: chloroform:methanol=3:1(v/v)), concentrated again, and then crystallized from dimethylether to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (0.71g).

$R_f$ = 0.41 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.73-1.76(m,2H), 2.31(s,3H), 2.33(s,3H), 2.61-2.70(m,8H), 3.69(1s,2H), 7.08(d,1H), 7.36-7.56(m,7H), 7.93-7.97(d,2H), 8.29(s,1H), 8.58-8.76 (m,3H), 9.37(s,1H), 10.17(s,1H)

Example 2

4-(4-Methylhomopiperazin-1-ylmethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (250mg, 0.429mmol) was dissolved in ethanol (10㎖), methanesulfonic acid (64㎕, 0.984mmol) was added, and the mixture was reacted at room temperature for 16 hours. The resulting solid was filtered and washed with acetone to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)

aminophenyl]benzamide methanesulfonate (230mg).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 166-168°C

$^1$H-NMR(DMSO-$d_6$)= 2.12(br,2H), 2.58(s,3H), 2.65(s,3H), 2.80(s,3H), 3.37 (m,4H), 3.62(m,4H), 4.33(s,2H), 7.05(d,1H), 7.16(s,3H), 7.41-7.43(d,2H), 7.67-7.79 (m,3H), 8.15(d,1H), 8.49(d,1H), 8.64(d,1H), 8.91(s,1H)

Example 3

N-[5-(4-chloromethylbenzoylamino)-2-methylphenyl]-4-(3-pyridyl)-2-pyrimidine-amine (1g, 2.33mmol) was dissolved in tetrahydrofuran (20mℓ), pyridine (360㎕, 4.66mmol) was added thereto, and the mixture was stirred for 30 minutes. 1-Amino-4-methylpiperazine (418㎕, 3.49mmol) was added, and the mixture was refluxed for 12 hours and filtered. The filtrate was concentrated, subjected to column chromatography (eluent: chloroform:methanol=3:1(v/v)), concentrated again, and then crystallized from dimethylether to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (880mg).

$R_f$ = 0.40 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR($CDCl_3$)= 2.31(d,6H), 7.48(br,8H), 3.54(s,2H), 7.06-7.42(m,8H), 7.79-7.83(d,2H), 8.07(s,1H), 8.46-8.68(m,4H), 9.20(m,1H)

Example 4

4-(4-Methylpiperazin-1-ylaminomethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (95mg, 0.187mmol) was dissolved in ethanol (8mℓ), methanesulfonic acid (24㎕, 0.347mmol) was added thereto, and the mixture was reacted at room temperature for 16 hours. The resulting solid was filtered and washed with acetone to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (80mg).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 144-146 °C

$^1$H-NMR($D_2O$)= 1.79(s,3H), 2.67(s,3H), 2.78-2.81(m,8H), 3.22(s,3H), 3.67(s,2H), 6.62(d,1H), 6.75-6.81(m,2H), 7.18-7.22(m,3H), 7.36-7.40(d,2H), 7.74 (s,1H), 7.86-7.89 (d,1H), 8.15-8.18(d,2H), 8.60(s,1H)

Preparation 3

N-(4-methyl-3-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (34g, 0.11mol) and stannous chloride dihydrate (124.5g, 0.55mol) were dissolved in a solvent mixture of ethyl acetate and ethanol (300㎖, 10/1, v/v) and reacted under reflux for 26 hours. The reaction mixture was cooled to room temperature, washed with 10% aqueous hydrochloric acid solution, concentrated, and subjected to column chromatography (chloroform/methanol= 9/1, v/v) to give N-(3-amino-4-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (32g).

$R_f$ = 0.48 (Methylene chloride : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.20(s,3H), 4.81(s,2H), 6.81-6.94(m,2H), 7.08(s,1H), 7.40-7.43(d,1H), 7.54-7.61(m,1H), 8.48-8.55(m,2H), 8.71-8.76(m,1H), 9.33-9.40 (d,1H)

The starting material was prepared as follows.

Step 3.1

4-Methyl-3-nitroaniline (90g, 0.592mol) was dissolved in ethanol (250㎖) and 65% aqueous nitric acid solution (59g, 0.592mol) was added thereto. When the exothermic reaction is stopped, cyanamide (74.6g) dissolved in water in a concentration of 50% was added. The brown mixture was reacted under reflux for 24 hours. The reaction mixture was cooled to 0°C, filtered, and washed with diethylether to give 4-methyl-3-nitrophenyl-guanidine nitrate (93g).

$R_f$ = 0.1 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.50(s,3H), 7.48-7.56(m,2H), 7.86(s,1H), 8.11-8.15(d,2H)

Step 3.2

3-Dimethylamino-1-(3-pyridyl)-2-propen-1-one (20g, 0.11mol), 4-methyl-3-nitrophenyl-guanidine nitrate (32g, 0.12mol), and sodium hydroxide (6.8g, 0.17mol) were dissolved in isopropanol, and reacted under reflux for 28 hours. The reaction solution was cooled to 0°C, filtered, washed with isopropanol, water and ethanol, and dried to give N-(4-methyl-3-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (32g).

$R_f$ = 0.76 (Methylene chloride : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.43(s,3H), 7.44-7.47(d,1H), 7.61-7.63(d,2H), 7.89-7.94 (d,1H), 8.55-8.59(d,1H), 8.69-8.71(d,1H), 8.77-8.79(m,1H), 8.86(s,1H), 9.41 (s,1H)

Preparation 4

N-(3-amino-4-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (11g, 39.8mmol) was dissolved in tetrahydrofuran (100㎖), triethylamine (8.3㎖, 59.5mmol) was added thereto, and the mixture was stirred for 30 minutes. 4-Chloromethyl benzoyl chloride (2.03g, 10.78mmol) was added, and the resulting mixture was reacted under reflux for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated and crystallized from methylene chloride to give N-(5-(4-chloromethylbenzoylamino)-4-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (5.3g).

$R_f$ = 0.86 (Methylene chloride : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.23(s,3H), 4.89(s,2H), 7.23-7.27(d,1H), 7.52-7.66(m,5H), 8.02-8.08(m,3H), 8.57-8.65(m,1H), 8.75-8.77(d,1H), 9.40(s,1H), 9.83(s,1H), 9.99(s,1H)

Example 5

N-(5-(4-chloromethylbenzoylamino)-4-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (1.5g, 3.49mmol) was dissolved in tetrahydrofuran (30㎖), pyridine (560㎕, 6.98mmol) was added, and the mixture was stirred for 30 minutes. N-methylhomo-

piperazine (660㎕, 5.23mmol) was added thereto, and the resulting mixture was refluxed for 12 hours and then filtered. The filtrate was concentrated and crystallized from dimethylether to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[2-methyl-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.2g).

$R_f$ = 0.12 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.98-2.03(m,2H), 2.33(s,3H), 2.47-2.99(m,8H), 3.15(s,3H), 4.27(s,2H), 7.16-7.19(m,3H), 7.23-7.26(d,1H), 7.41-7.53(m,4H), 7.79-7.89(m,3H), 8.44-8.53(m,2H), 8.70-8.72(d,1H), 9.27(s,1H)

Example 6

4-(4-Methylhomopiperazin-1-ylmethyl)-N-[2-methyl-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.2g, 2.29mmol) was dissolved in ethanol (18㎖), methanesulfonic acid (149㎕, 2.29mmol) was added, and the mixture was reacted at room temperature for 18 hours. The resulting solid was filtered and washed with acetone to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[2-methyl-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (1.03g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 168-170 °C

$^1$H-NMR($D_2O$)= 2.14(m,2H), 2.67(d,6H), 2.88(s,3H), 3.23-3.51(m,8H), 3.70 (s,2H), 7.25-7.34(m,3H), 7.46(s,1H), 7.57-7.90(m,6H), 8.70-8.74(m,1H), 8.98-9.01 (m,1H), 9.24(s,1H)

Example 7

N-(5-(4-chloromethylbenzoylamino)-4-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (1.5g, 3.49mmol) was dissolved in tetrahydrofuran (30㎖), pyridine (560㎕, 6.98mmol) was added, and the mixture was stirred for 30 minutes. 1-Amino-4-methylpiperazine (580㎕, 5.23mmol) was added thereto, and the resulting mixture was

refluxed for 12 hours and then filtered. The filtrate was concentrated and crystallized from dimethylether to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[2-methyl-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.7g).

$R_f$ = 0.39 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.22(d,6H), 2.53(m,8H), 3.42(s,2H), 7.21-7.26(m,1H), 7.46-7.64(m,7H), 7.98-8.02(d,2H), 8.57-8.63(m,3H), 8.73-8.75(d,1H), 9.39(s,1H), 9.82-9.92(d,1H)

Example 8

4-(4-Methylpiperazin-1-ylaminomethyl)-N-[2-methyl-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.7g, 3.42mmol) was dissolved in ethanol (25㎖), methanesulfonic acid (222㎕, 3.42mmol) was added, and the mixture was reacted at room temperature for 18 hours. The resulting solid was filtered and washed with acetone to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[2-methyl-5-(4-(pyridin-3-yl)pyrimidin-2-yl) aminophenyl]benzamide methanesulfonate (1.43g).

$R_f$ = 0.17 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 150-152 °C

$^1$H-NMR($D_2O$)= 2.12(s,3H), 2.66(d,6H), 2.92(s,3H), 3.59(m,8H), 4.46(s,2H), 7.16-7.27(m,2H), 7.33-7.35(d,1H), 7.43(s,1H), 7.50-7.62(d,2H), 7.89-8.03(m,3H), 8.33-8.36(d,1H), 8.72-8.75(d,1H), 8.98-9.02(d,1H), 9.23(s,1H)

Preparation 5

N-(4-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine was reacted according to the same procedure as Preparation 1 to give N-(4-aminophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (7.1g).

$R_f$ = 0.5 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 4.84(s,2H), 6.55-6.59(d,2H), 7.34-7.41(t,3H), 7.54-7.61 (m,1H), 8.44-8.50(m,2H), 8.70-8.73(m,1H), 9.27-9.31(m,2H)

Step 5.1

4-Nitroaniline (30g, 0.22mol) and cyanamide (water 50%) (27.4g, 0.33mol) were reacted according to the same procedure as Step 1.2 of Preparation 1 to give 4-nitrophenyl-guanidine nitrate (29.1g).

$R_f$ = 0.1 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

$^1$H-NMR(DMSO-$d_6$)= 7.46-7.50(d,2H), 7.90(br,4H), 8.28-8.32(d,2H)

Step 5.2

4-Nitrophenyl-guanidine nitrate (20g, 0.08mol) and 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (11.75g, 0.06mol) were reacted according to the same procedure as Step 1.3 of Preparation 1 to give N-(4-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (9.38g).

$R_f$ = 0.7 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 7.59-7.62(m,1H), 7.72(d,1H), 8.07-8.12(d,2H), 8.24-8.28 (d,2H), 8.54-8.58(m,1H), 8.73-8.77(m,2H), 9.38(s,1H), 10.62(s,1H)

Preparation 6

4-(Chloromethyl)benzoylchloride (10g, 53mmol) was reacted according to the same procedure as Preparation 2 to give N-(4-(4-chloromethylbenzoylamino)phenyl)-4-(3-pyridyl)-2-pyrimidine-amine (13.2g).

$R_f$ = 0.6 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 4.88(s,2H), 7.45-7.51(m,3H), 7.55-7.64(m,1H), 7.71-7.73 (m,4H), 7.85-7.89(m,2H), 8.43-8.55(m,2H), 8.71(d,1H), 9.30(s,1H), 9.71(s,1H),

10.03(s,1H)

Example 9

1-Methylhomopiperazine (3.45g, 30.2mmol) was reacted according to the same procedure as Example 1 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (3.7g).

$R_f$ = 0.4 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.69-1.74(m,2H), 2.24(s,3H), 2.45-2.67(m,8H), 3.67(s,2H), 7.43-7.50(m,3H), 7.56-7.63(m,1H), 7.74-7.77(m,4H), 7.89-7.93(m,2H), 8.49-8.61 (m,2H), 8.73(d,1H), 9.34(s,1H), 9.76(s,1H), 10.16(s,1H)

Example 10

Methanesulfonic acid (0.58g, 6mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (1.47g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 152-154 °C

$^1$H-NMR($D_2O$)= 1.69(m,2H), 2.67(s,3H), 2.81(s,3H), 3.05(m,2H), 3.28-3.44 (m,6H), 3.96(s,2H), 6.93-6.96(m,1H), 7.16-7.38(m,7H), 7.60-7.64(m,2H), 8.11-8.13 (m,2H), 8.40(m,1H), 8.70(s,1H)

Preparation 7

N-(3-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (24g, 0.08mol) was reacted according to the same procedure as Preparation 1 to give N-(3-aminophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (15.5g).

$R_f$ = 0.5 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 5.03(s,2H), 6.22-6.23(m,1H), 6.89-6.96(m,2H), 7.08(s,1H), 7.45(d,1H), 7.55-7.62(m,1H), 8.49-8.58(m,2H), 8.72-8.74(m,1H), 9.34(s,1H), 9.47 (s,1H)

Step 7.1

3-Nitroaniline (42g, 0.3mol) and cyanamide (water 50%) (38.4g, 0.46mol) were reacted according to the same procedure as Step 1.2 of Preparation 1 to give 3-nitrophenyl-guanidine nitrate (33.4g).

$R_f$ = 0.1 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

$^1$H-NMR(DMSO-$d_6$)= 7.75-7.81(m,5H), 8.14-8.17(d,2H)

Step 7.2

3-Nitrophenyl-guanidine nitrate (28g, 0.12mol) and 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (16.9g, 0.09mol) were reacted according to the same procedure as Step 1.3 of Preparation 1 to give N-(3-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (18.4g).

$R_f$ = 0.7 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 7.58-7.67(m,3H), 7.82-7.87(m,1H), 8.08-8.12(m,1H), 8.56-8.60(m,1H), 8.71-8.78(m,2H), 9.11(s,1H), 9.42-9.43(d,1H), 10.38(s,1H)

Preparation 8

4-(Chloromethyl)benzoylchloride (10g, 53mmol) was reacted according to the same procedure as Preparation 2 to give N-[3-(4-chloromethylbenzoylamino)phenyl]-4-(3-pyridyl)-2-pyrimidine-amine (15.34g).

$R_f$ = 0.6 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 4.88(s,2H), 7.33(br,2H), 7.53-7.64(m,5H), 7.99-8.03 (d,2H), 8.48(s,1H), 8.62-8.75(m,2H), 9.40(s,1H), 9.85(s,1H), 10.32(s,1H)

Example 11

1-Methylhomopiperazine (1.08g, 9.5mmol) was reacted according to the same procedure as Example 1 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (2.8g).

$R_f$ = 0.4 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.73-1.75(m,2H), 2.15(s,3H), 2.51-2.69(m,8H), 3.69(s,2H), 7.31(s,2H), 7.46-7.61(m,6H), 7.93-7.96(d,2H), 8.46(s,1H), 8.66-8.75(m,2H), 9.40 (s,1H), 9.82(s,1H), 10.24(s,1H)

Example 12

Methanesulfonic acid (0.24g, 2.5mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.78g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 206-208 °C

$^1$H-NMR($D_2O$)= 2.15-2.17(m,2H), 2.62(s,3H), 2.82(s,3H), 3.41-3.65(m,8H), 4.40(s,2H), 7.12-7.15(m,1H), 7.17-7.29(m,3H), 7.51-7.54(m,2H), 7.78-7.93(m,4H), 8.30-8.33(m,1H), 8.53(s,1H), 9.03(s,1H), 9.21(s,1H)

Example 13

1-Amino-4-methylpiperazine (1g, 8.7mmol) was reacted according to the same procedure as Example 3 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.7g).

$R_f$ = 0.4 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.16(s,3H), 2.37-2.39(m,8H), 3.54(s,2H), 7.31(m,2H),

7.44-7.54(m,6H), 7.92-7.96(m,2H), 8.45(br,1H), 8.61-8.74(m,3H), 9.36(s,1H), 9.81 (s,1H), 10.23(s,1H)

Example 14

Methanesulfonic acid (48mg, 0.5mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.23g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp=148-150°C

$^1$H-NMR($D_2O$)= 2.68(s,3H), 2.89(s,3H), 3.42-3.51(m,8H), 4.36(s,2H), 7.10 (m,2H), 7.32-7.38(m,3H), 7.54-7.57(d,2H), 7.86-7.93(m,3H), 8.00-8.08(m,1H), 8.46 (d,1H), 8.75(d,1H), 9.07(d,1H), 9.32(s,1H)

Preparation 9

N-(2-methyl-4-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (23g, 0.075mol) was reacted according to the same procedure as Preparation 1 to give N-(2-methyl-4-aminophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (21g).

$R_f$ = 0.5 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.08(s,3H), 4.97(s,2H), 6.40-6.46(m,2H), 7.01(d,1H), 7.29(d,1H), 7.53-7.56(m,1H), 8.37-8.42(m,2H), 8.65-8.70(m,2H), 9.21(s,1H)

Step 9.1

2-Methyl-4-nitroaniline (90g, 0.59mol) and cyanamide (water 50%) (74.6g, 0.88mol) were reacted according to the same procedure as Step 1.2 of Preparation 1 to give 2-methyl-4-nitrophenyl-guanidine nitrate (95g).

$R_f$ = 0.1 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.43(s,3H), 7.43-7.55(m,2H), 7.77(s,1H), 8.21-8.25(d,2H)

Step 9.2

2-Methyl-4-nitrophenyl-guanidine nitrate (26.3g, 0.1mol) and 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (15g, 0.08mol) were reacted according to the same procedure as Step 1.3 of Preparation 1 to give N-(2-methyl-4-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine -amine (15g).

$R_f$ = 0.7 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.44(s,3H), 7.58-7.66(m,2H), 8.16-8.19(m,3H), 8.48(d,1H), 8.65-8.74(m,2H), 9.31-9.32(m,2H)

Preparation 10

4-(Chloromethyl)benzoylchloride (10g, 0.053mol) was reacted according to the same procedure as Preparation 2 to give N-(4-(4-chloromethylbenzoylamino)-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine-amine (7g).

$R_f$ = 0.6 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.44(s,3H), 5.04(s,2H), 7.58-7.86(m,7H), 8.15(d,2H), 8.57 (d,1H), 8.61(d,1H), 8.69(d,1H), 8.88(s,1H), 9.43(s,1H), 10.43(s,1H)

Example 15

1-Methylhomopiperazine (1g, 9.5mmol) was reacted according to the same procedure as Example 1 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[3-methyl-4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (2.31g).

$R_f$ = 0.4 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.81-1.84(m,2H), 2.25(s,3H), 2.45(s,3H), 2.67-2.84(m,8H), 3.71(s,2H), 7.40-7.92(m,7H), 7.93-7.96(d,2H), 8.48-8.51(m,2H), 8.69(d,1H), 8.98 (s,1H),

9.25(s,1H), 10.19(s,1H)

Example 16

Methanesulfonic acid (0.24g, 2.5mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[3-methyl-4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.63g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 166-168 °C

$^1$H-NMR($D_2O$)= 1.97(s,3H), 2.10-2.17(m,2H), 2.68(s,3H), 2.79(s,3H), 2.95 (m,2H), 3.17(m,2H), 3.33-3.38(m,4H), 3.86(s,2H), 6.85(d,1H), 7.10(m,2H), 7.23-7.32(m,4H), 7.55(d,2H), 8.03-8.06(m,2H), 8.37(d,1H), 8.63(s,1H)

Example 17

1-Amino-4-methylpiperazine (1g, 9mmol) was reacted according to the same procedure as Example 3 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[3-methyl-4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.2g).

$R_f$ = 0.4 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.15(s,3H), 2.25(s,3H), 2.36(m,8H), 3.53(s,2H), 7.40-7.68 (m,7H), 7.91-7.95(m,3H), 8.39-8.60(m,2H), 8.69-8.71(m,1H), 8.98(s,1H), 9.26 (s,1H), 10.18(s,1H)

Example 18

Methanesulfonic acid (48mg, 0.5mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[3-methyl-4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.17g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 172-174 °C

$^1$H-NMR($D_2O$)= 1.19(s,3H), 2.65(s,3H), 2.67(s,3H), 2.85-2.88(m,4H), 3.01-3.11(m,4H), 3.45(s,2H), 6.77(d,1H), 6.98-7.27(m,6H), 7.43(d,2H), 7.95(m,1H), 7.99(d,1H), 8.21-8.24(m,1H), 8.54(s,1H)

Preparation 11

N-(2-methoxy-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (22g, 0.068mol) was reacted according to the same procedure as Preparation 1 to give N-(2-methoxy-5-aminophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (10g).

$R_f$ = 0.5 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 3.74(s,3H), 4.75(s,2H), 6.24-6.28(m,1H), 6.75-6.80(m,1H), 7.48-7.60(m,3H), 8.01(s,1H), 8.50-8.58(m,2H), 8.72-8.74(m,1H), 9.34(s,1H)

Step 11.1

2-Methoxy-5-nitroaniline (90g, 0.535mol) and cyanamide (water 50%) (67.5g, 0.803mol) were reacted according to the same procedure as Step 1.2 of Preparation 1 to give 2-methoxy-5-nitrophenyl-guanidine nitrate (74g).

$R_f$ = 0.1 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

$^1$H-NMR(DMSO-$d_6$)= 3.97(s,3H), 7.35-7.45(m,4H), 8.13(m,1H), 8.24-8.30(m,1H)

Step 11.2

2-Methoxy-5-nitrophenyl-guanidine nitrate (31g, 0.113mol) and 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (20g, 0.113mol) were reacted according to the same procedure as Step 1.3 of Preparation 1 to give N-(2-methoxy-5-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (23g).

$R_f$ = 0.7 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 4.03(s,3H), 5.25(s,1H), 7.24(d,1H), 7.29(d,1H), 7.55-7.67(m,3H), 7.94-8.00(m,1H); 8.54(m,1H), 8.58-8.76(m,1H), 9.38(s,1H)

Preparation 12

4-(Chloromethyl)benzoylchloride (4.6g, 0.053mol) was reacted according to the same procedure as Preparation 2 to give N-[5-(4-chloromethylbenzoylamino)-2-methoxy-phenyl]-4-(3-pyridyl)-2-pyrimidine-amine (4.4g).

$R_f$ = 0.6 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 3.87(s,3H), 4.87(s,2H), 7.07(d,1H), 7.36-7.41(m,1H), 7.52-7.63(m,4H), 7.99(d,2H), 8.31(s,1H), 8.58-8.78(m,4H), 9.39(s,1H), 10.25 (s,1H)

Example 19

1-Methylhomopiperazine (1.05㎖, 8.42mmol) was reacted according to the same procedure as Example 1 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-methoxy-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.1g).

$R_f$ = 0.2 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.74-1.83(m,2H), 2.30(s,3H), 2.66-2.74(m,8H), 3.69(s,2H), 3.87(s,3H), 7.07(d,1H), 7.35-7.56(m,5H), 7.94(d,2H), 8.29(s,1H), 8.58-8.76 (m,4H), 9.38(s,1H), 10.17(s,1H)

Example 20

Methanesulfonic acid (0.18g, 1.91mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-methoxy-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.3g).

$R_f$ = 0.5 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 140-142 °C

$^1$H-NMR($D_2O$)= 2.20(br,2H), 2.66(s,3H), 2.88(s,3H), 3.49(m,8H), 3.71(s,3H), 4.42(s,2H), 6.49(s,2H), 6.87-6.89(m,1H), 7.48-7.52(m,2H), 7.63-7.67(m,3H), 7.88-7.90(m,1H), 8.21(s,1H), 8.45(m,1H), 8.71(m,1H), 8.91(s,1H)

Example 21

N-[5-(4-chloromethylbenzoylamino)-2-methoxy-phenyl]-4-(3-pyridyl)-2-pyrimidine-amine (1.4g, 3.14mmol) and 1-amino-4-methylpiperazine (0.94㎖, 7.86 mmol) were reacted according to the same procedure as Example 3 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-methoxy-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (0.12g).

$R_f$ = 0.2 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.67(s,3H), 2.85-2.88(m,8H), 3.66(s,2H), 3.96(s,3H), 6.89-6.93(d,2H), 7.19(d,1H), 7.34-7.46(m,4H), 7.85-7.94(m,4H), 8.54-8.59(m,1H), 8.71-8.73(m,1H), 8.91(s,1H), 9.28(s,1H)

Example 22

Methanesulfonic acid (0.24g, 2.5mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-methoxy-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.67g).

$R_f$ = 0.5 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 142-144 °C

$^1$H-NMR($D_2O$)= 2.69(s,3H), 2.93(s,3H), 3.38-3.51(m,8H), 3.62(s,3H), 4.40 (s,2H), 6.69(br,2H), 7.09-7.12(m,1H), 7.54-7.57(m,2H), 7.75-7.88(m,3H), 8.12- 8.14(m,1H), 8.30(s,1H), 8.61-8.63(m,1H), 8.93-8.96(m,1H), 9.12(s,1H)

Preparation 13

N-(4-fluoro-3-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (22g, 0.068mol) was reacted according to the same procedure as Preparation 1 to give N-(4-fluoro-3-aminophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (14g).

$R_f$ = 0.5 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 5.12(s,2H), 6.91(d,2H), 7.22(d,1H), 7.43(d,1H), 7.54-7.61 (m,1H), 8.48-8.56(m,2H), 8.70-8.73(m,1H), 9.32(s,1H), 9.51(s,1H)

Step 13.1

4-Fluoro-3-nitroaniline (100g, 0.64mol) and cyanamide (water 50%) (80.8g, 0.96mol) were reacted according to the same procedure as Step 1.2 of Preparation 1 to give 4-fluoro-3-nitrophenyl-guanidine nitrate (74g).

$R_f$ = 0.1 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

$^1$H-NMR(DMSO-$d_6$)= 7.64-7.83(m,6H), 8.06-8.10(m,1H)

Step 13.2

4-Fluoro-3-nitrophenyl-guanidine nitrate (40g, 0.153mol) and 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one (27g, 0.153mol) were reacted according to the same procedure as Step 1.3 of Preparation 1 to give N-(4-fluoro-3-nitrophenyl)-4-(3-pyridyl)-2-pyrimidine-amine (30g).

$R_f$ = 0.7 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 7.23(d,1H), 7.51-7.63(m,3H), 7.78-7.99(m,1H), 8.52-8.73 (m,3H), 9.41(s,1H), 10.28(s,1H)

Preparation 14

4-(Chloromethyl)benzoylchloride (4.6g, 0.053mol) was reacted according to the

same procedure as Preparation 2 to give N-[3-(4-chloromethylbenzoylamino)-4-fluoro-phenyl)-4-(3-pyridyl)-2-pyrimidine-amine (3.5g).

$R_f$ = 0.6 (Chloroform : Methanol = 9 : 1)

$^1$H-NMR(DMSO-$d_6$)= 4.48(s,2H), 7.28(br,2H), 7.53-7.65(m,4H), 8.01(d,2H), 8.21-8.25(m,1H), 8.61-8.63(m,2H), 8.73(d,1H), 9.37(s,1H), 9.91(s,1H), 10.21 (s,1H)

Example 23

1-Methylhomopiperazine (0.66g, 5.77mmol) was reacted according to the same procedure as Example 1 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[2-fluoro-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.02g).

$R_f$ = 0.2 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 1.70-1.78(m,2H), 2.26(s,3H), 2.51-2.69(m,8H), 3.69(s,2H), 7.27-7.32(m,1H), 7.51-7.68(m,6H), 7.96-8.00(m,1H), 8.59-8.75(m,2H), 9.37(s,1H), 9.91(s,1H), 10.12(s,1H)

Example 24

Methanesulfonic acid (50mg, 0.52mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[2-fluoro-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.21g).

$R_f$ = 0.5 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 125-127 °C

$^1$H-NMR($D_2O$)= 1.91(m,2H), 2.67(s,3H), 2.76(s,3H), 2.97(m,4H), 3.28(m,4H), 3.69(s,2H), 6.55-6.64(m,3H), 6.81-6.85(m,1H), 7.18-7.23(d,2H), 7.41-7.46(d,2H), 7.61(m,1H), 7.72-7.75(m,2H), 7.91(m,1H), 8.31(s,1H)

Example 25

1-Methylpiperazine (0.58g, 5.77mmol) and N-[4-fluoro-3-(4-chloromethylbenzoyl amino)-phenyl]-4-(3-pyridyl)-2-pyrimidine-amine (1g, 2.31mmol) were reacted according to the same procedure as Example 1 to give 4-(4-methylpiperazin-1-ylmethyl)-N-[2-fluoro-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.1g).

$R_f$ = 0.2 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.28(s,3H), 2.51(s,8H), 3.57(s,2H), 7.27-7.31(m,1H), 7.45-7.67(m,5H), 7.97-8.01(d,2H), 8.17(m,1H), 8.56-8.74(m,3H), 9.36(s,1H), 9.90 (s,1H), 10.14(s,1H)

Example 26

Methanesulfonic acid (0.58g, 6mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylpiperazin-1-ylmethyl)-N-[2-fluoro-5-(4-pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (1.53g).

$R_f$ = 0.5 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 174-176 °C

$^1$H-NMR($D_2O$)= 2.67(s,3H), 2.76(s,3H), 2.82(m,4H), 3.22(m,4H), 3.70(s,2H), 6.64-6.77(m,3H), 7.27-7.31(m,3H), 7.51(d,2H), 7.63(d,1H), 7.86(d,1H), 8.18 (d,2H), 8.58(s,1H)

Example 27

1-Amino-4-methylpiperazine (0.66g, 5.77mol) and N-[4-fluoro-3-(4-chloromethyl benzoylamino)-phenyl]-4-(3-pyridyl)-2-pyrimidine-amine (1g, 2.31mmol) were reacted according to the same procedure as Example 3 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[2-fluoro-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (0.63g).

$R_f$ = 0.2 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.15(s,3H), 2.37-2.41(m,8H), 3.55(s,2H), 7.27(m,1H), 7.45-7.67(m,6H), 7.95(d,2H), 8.21(m,1H), 8.55-8.74(m,3H), 9.36(s,1H), 9.90 (s,1H), 10.12(s,1H)

Example 28

Methanesulfonic acid (0.18g, 1.91mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[2-fluoro-5-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.27g).

$R_f$ = 0.5 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 142-144 °C

$^1$H-NMR($D_2O$)= 2.67(s,3H), 2.83(s,3H), 3.17-3.37(m,8H), 4.06(s,2H), 6.95-7.01 (m,2H), 7.11(d,1H), 7.45(d,2H), 7.74-7.79(m,3H), 7.87-7.91(m,1H), 8.21 (d,1H), 8.55 (d,1H), 8.73(d,1H), 9.05(s,1H)

Example 29

1-Amino-4-methylpiperazine (1g, 8.7mmol) was reacted according to the same procedure as Example 3 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.23g).

$R_f$ = 0.4 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(DMSO-$d_6$)= 2.27(s,3H), 2.39-2.57(m,8H), 3.91(s,2H), 7.47-7.53(m,4H), 7.56-7.66(m,1H), 7.77-7.88(m,4H), 7.91-7.93(m,2H), 8.50-8.61(m,2H), 8.80(d,1H), 9.35(s,1H), 9.79(s,1H), 10.17(s,1H)

Example 30

Methanesulfonic acid (48mg, 0.5mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.17g).

$R_f$ = 0.2 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 151-153 °C

$^1$H-NMR($D_2O$)= 2.71(s,3H), 2.81(s,3H), 3.21-3.23(m,4H), 3.31-3.41(m,4H), 3.99(s,2H), 6.91-6.94(m,1H), 7.11-7.31(m,7H), 7.60-7.63(m,2H), 8.13-8.17(m,2H), 8.43(m,1H), 8.73(s,1H)

Example 31

1-Methylpiperazine (1.2㎖, 10.38mmol) was reacted according to the same procedure as Example 3 to give 4-(4-methylpiperazin-1-ylmethyl)-N-[4-fluoro-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (1.3g).

$R_f$ = 0.2 (Chloroform : Methanol = 1 : 1 )

$^1$H-NMR(MeOD)= 2.67(m,8H), 3.03(s,3H), 3.69(s,2H), 7.16-7.21(m,2H), 7.43-7.59(m,4H), 7.93-7.97(d,2H), 8.53-8.56(d,1H), 8.63-8.69(m,3H), 9.31(s,1H)

Example 32

Methanesulfonic acid (186㎕, 2.87mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylmethyl)-N-[4-fluoro-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (790mg).

$R_f$ = 0.21 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 172-174 °C

$^1$H-NMR($D_2O$)= 2.70(s,3H), 2.87(s,3H), 3.12(m,4H), 3.38(m,4H), 3.96(s,2H),

6.46(br,1H), 6.58-6.69(m,1H), 6.83-6.86(d,1H), 7.29-7.43(m,5H), 7.88-7.90(d,1H), 8.10-8.13(m,1H), 8.23-8.25(d,1H), 8.40-8.44(d,1H), 8.72(s,1H)

Example 33

1-Methylhomopiperazine (1.3㎖, 10.38mmol) was reacted according to the same procedure as Example 1 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-fluoro-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide (580mg).

$R_f$ = 0.1 (Chloroform : Methanol = 1 : 1)

$^1$H-NMR(MeOD)= 1.96-2.00(m,2H), 2.70(s,3H), 2.76-2.87(m,4H), 3.06-3.19 (m,4H), 3.78(s,2H), 7.18(m,1H), 7.43-7.46(m,1H), 7.52-7.59(m,4H), 7.92-7.96 (d,2H), 8.54-8.56(d,1H), 8.63-8.70(m,3H), 9.32(s,1H)

Example 34

Methanesulfonic acid (75.3㎕, 1.16mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-fluoro-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (790mg).

$R_f$ = 0.13 (Methylene chloride : Ethyl acetate : Methanol : 25% Aqueous ammonia = 60 : 10 : 30 : 1)

mp = 158-160 °C

$^1$H-NMR($D_2O$)= 2.18(br,2H), 2.67(s,3H), 2.88(s,3H), 3.38-3.45(m,4H), 3.65-3.71(m,4H), 4.34(s,2H), 6.56(m,1H), 6.74-6.84(m,1H), 6.89-6.92(d,1H), 7.21-7.28 (m,1H), 7.42-7.46(d,2H), 7.56-7.60(d,2H), 7.67-8.00(d,1H), 8.18-8.30(m,3H), 8.71 (s,1H)

Example 35

Piperidine (1.5g, 17.6mmol) was reacted according to the same procedure as Example 1 to give 4-(piperidin-1-ylmethyl)-N-[3-(4-(pyridin-3-yl)pyrimidin-2-yl)amino-phenyl]benzamide (2.2g).

$R_f$ = 0.43 (Chloroform : Methanol = 1 : 1 )

$^1$H-NMR(DMSO-$d_6$)= 2.17(s,3H), 2.53-2.81(m,10H), 3.71(s,2H), 7.33(s,2H), 7.51-7.63(m,6H), 7.95-7.99(d,2H), 8.47(s,1H), 8.49-8.77(m,2H), 9.43(s,1H), 9.89(s,1H), 10.19(s,1H)

Example 36

Methanesulfonic acid (0.248g, 2.5mmol) was reacted according to the same procedure as Example 2 to give 4-(piperidin-1-ylmethyl)-N-[3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide methanesulfonate (0.83g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 173-175 °C

$^1$H-NMR($D_2O$)= 2.63(s,3H), 2.81(s,3H), 3.41-3.53(m,4H), 3.61-3.69(m,6H), 4.31(s,2H), 7.11-7.15(m,1H), 7.21-7.31(m,3H), 7.53-7.57(m,2H), 7.81-7.95(m,4H), 8.33-8.37(m,1H), 8.55(s,1H), 9.07(s,1H), 9.22(s,1H)

Example 37

Acetic acid (0.58g, 9.2mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-(4-(pyridin-3-yl) pyrimidin-2-yl)aminophenyl]benzamide acetate (1.53g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 197-199

$^1$H-NMR($D_2O$)= 1.68(m,2H), 2.53(s,3H), 2.67(s,3H), 3.01-3.06(m,2H), 3.33-3.47(m,6H), 3.99(s,2H), 6.95-6.99(m,1H), 7.16-7.37(m,7H), 7.61-7.65(m,2H), 8.11-8.15(m,2H), 8.41(m,1H), 8.69(s,1H)

Example 38

Acetic acid (0.24g, 3.8mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide acetate (0.61g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 165-167 °C

$^1$H-NMR($D_2O$)= 2.07(s,2H), 2.58(s,3H), 2.61(s,3H), 2.77(s,3H), 3.41(m,4H), 3.63(m,4H), 4.41(s,2H), 7.01(d,1H), 7.17(s,3H), 7.38-7.41(d,2H), 7.63-7.75 (m,3H), 8.20(d,1H), 8.47(d,1H), 8.61(d,1H), 8.93(s,1H)

Example 39

Acetic acid (0.18g, 2.8mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide acetate (0.31g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 153-155 °C

$^1$H-NMR($D_2O$)= 1.37(s,3H), 2.53(s,3H), 2.67(s,3H), 2.83-2.88(m,4H), 2.97-3.11(m,4H), 3.43(s,2H), 6.79(d,1H), 6.99-7.27(m,6H), 7.41(d,2H), 7.99(m,1H), 8.02(d,1H), 8.22-8.27(m,1H), 8.57(s,1H)

Example 40

Acetic acid (0.3g, 4.7mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-(4-(pyridin-3-yl) pyrimidin-2-yl)aminophenyl]benzamide acetate (0.57g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 169-171 °C

$^1$H-NMR($D_2O$)= 2.65(s,3H), 2.78(s,3H), 3.20-3.25(m,4H), 3.30-3.43(m,4H),

4.00(s,2H), 6.87-6.95(m,1H), 7.11-7.38(m,7H), 7.61-7.65(m,2H), 8.15-8.19(m,2H), 8.43(m,1H), 8.81(s,1H)

Example 41

Hydrochloric acid (2.2g, 60.2mmol) was reacted according to the same procedure as Example 2 to give 4-(4-methylhomopiperazin-1-ylmethyl)-N-[4-(4-(pyridin-3-yl) pyrimidin-2-yl)aminophenyl]benzamide hydrochloride (0.83g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 197-199 °C

$^1$H-NMR($D_2O$)= 1.77(m,2H), 2.43(s,3H), 3.00-3.07(m,2H), 3.31-3.43(m,6H), 4.01(s,2H), 7.03-7.15(m,1H), 7.19-7.33(m,7H), 7.71-7.83(m,2H), 8.15-8.18(m,2H), 8.41(m,1H), 8.71(s,1H)

Example 42

Hydrochloric acid (1.3g, 35.6mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-yl)aminophenyl]benzamide hydrochloride (0.21g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 173-175 °C

$^1$H-NMR($D_2O$)= 1.77(s,3H), 2.55(s,3H), 2.85-2.93(m,4H), 2.97-3.11(m,4H), 3.51(s,2H), 6.81(d,1H), 7.00-7.25(m,6H), 7.43(d,2H), 8.00(m,1H), 8.05(d,1H), 8.25-8.33 (m,1H), 8.63(s,1H)

Example 43

Hydrochloric acid (2.5g, 68.4mmol) was reacted according to the same procedure as Example 4 to give 4-(4-methylpiperazin-1-ylaminomethyl)-N-[4-(4-(pyridin-3-yl) pyrimidin-2-yl)aminophenyl]benzamide hydrochloride (0.43g).

$R_f$ = 0.2 (Methylene chloride : Methanol : 25% Aqueous ammonia = 150 : 10 : 1)

mp = 183-185 °C

$^1$H-NMR($D_2O$)= 2.67(s,3H), 3.21-3.30(m,4H), 3.33-3.47(m,4H), 4.07(s,2H), 6.85-6.95(m,1H), 7.13-7.47(m,7H), 7.63-7.68(m,2H), 8.17-8.21(m,2H), 8.47(m,1H), 8.88(s,1H)

Experiment 1

In the present experiment, the inhibitory activity of the compound of formula (1) was determined against the growth of K562 cancer cell. First, the cells were allowed to stand in RPMI (Roswell Park Memorial Institute)-1640 medium containing 10%(v/v) fetal bovine serum in an incubator of 37°C and 5% by volume of $CO_2$. The cancer cells (1000 cells) were transferred to a 96-well plate, and the test compound was diluted. The plate was allowed to stand under the above mentioned conditions for 2 days. After this treatment, to the cells was added 0.2% MTT (3-[4,5-dimethylthiazol- 2-yl]-2,5-diphenyltetrazolium bromide) solution, and the resulting mixture was allowed to stand for 4 hours. The supernatant was removed to leave the resulting crystal. DMSO was added to dissolve the crystal, and the absorbance of the solution was measured at 540nm. $IC_{50}$ value was calculated using a computer system according to the following formula:

$$(OD_{540}(test)-OD_{540}(initial)/OD_{540}(control)-OD_{540}(initial)) \times 100$$

In the present experiment, the $IC_{50}$ value is defined as the concentration of the active compound when the number of cells per well at the end of constant temperature-treatment is 50% of the number of cells in the control medium.

The $IC_{50}$ values [$\mu g/m\ell$] in the following Table 1 were measured to the example compounds according to the present invention.

Table 1

| Example No. | $IC_{50}$ [$\mu g/m\ell$] |
|---|---|
| Imatinib mesylate | 0.54 |
| 2 | 1.20 |
| 4 | <0.10 |
| 6 | 20.51 |
| 8 | 27.58 |
| 10 | 3.85 |
| 12 | 10.21 |
| 14 | 8.95 |
| 16 | >50.0 |
| 20 | 34.7 |
| 22 | 10.0 |
| 24 | 19.05 |
| 28 | 8.63 |
| 30 | 22.81 |
| 32 | 8.06 |
| 34 | 7.17 |
| 36 | 11.32 |
| 41 | 5.61 |
| 42 | 0.30 |
| 43 | >50.0 |

As can be seen in the above Table 1, the existing drug of Imatinib mesylate showed an $IC_{50}$ value of 0.54$\mu g/m\ell$ against the CML cell line, K562, whereas the compound of Example 4 of the present invention showed an $IC_{50}$ value of 0.1$\mu g/m\ell$ or less, which corresponds to 5 times improved activity. Further, the compound of Example 42 showed much higher activity than Imatinib mesylate.

Experiment 2

In the present experiment, the inhibitory activity of the compound of formula (1) was determined against the growth of L1210 cancer cell. The test was performed according to the same procedure as Experiment 1. Thus obtained $IC_{50}$ values [$\mu g/m\ell$] are represented in the following Table 2.

Table 2.

| Example No. | $IC_{50}$ [$\mu g/m\ell$] |
|---|---|
| Imatinib mesylate | 32.90 |
| 2 | 7.60 |
| 4 | 26.90 |
| 6 | 3.24 |
| 8 | 7.38 |
| 10 | 3.40 |
| 12 | 0.99 |
| 20 | 4.32 |
| 22 | 4.46 |
| 36 | 5.95 |

As can be seen in the above Table 2, the existing drug of Imatinib mesylate showed an $IC_{50}$ value of 32.90$\mu g/m\ell$ against the leukemia cell line, L1210, whereas the compounds of Examples 12 and 6 of the present invention showed $IC_{50}$ values of 0.99$\mu g/m\ell$ and 3.24$\mu g/m\ell$, respectively, which corresponds to 32 times and 10 times improved activity, respectively. Further, all the other example compounds showed much higher activity than Imatinib mesylate.

Experiment 3

In the present experiment, the inhibitory activity of the compound of formula (1) was determined against the growth of U937 cancer cell. The test was performed according to the same procedure as Experiment 1. Thus obtained $IC_{50}$ values [$\mu g/m\ell$] are represented in the following Table 3.

Table 3.

| Example No. | $IC_{50}$ [$\mu g/m\ell$] |
|---|---|
| Imatinib mesylate | 28.75 |
| 2 | 0.70 |
| 4 | 0.90 |
| 6 | 5.14 |
| 8 | 9.44 |
| 10 | 7.30 |
| 12 | 3.41 |
| 20 | 9.51 |
| 22 | 8.61 |
| 36 | 6.91 |

As can be seen in the above Table 3, the existing drug of Imatinib mesylate showed an $IC_{50}$ value of 28.75$\mu g/m\ell$ against the monocyte like leukemia cell line, U937, whereas the compounds of Examples 2 and 4 of the present invention showed $IC_{50}$ values of 0.7$\mu g/m\ell$ and 0.9$\mu g/m\ell$, respectively, which corresponds to 40 times and 30 times improved activity, respectively. Further, all the other example compounds showed much higher activity than Imatinib mesylate.

Experiment 4

In the present experiment, the inhibitory activity of Imatinib mesylate and the compounds of Examples 2, 4, and 10 were determined against the growth of several cancer cells. The test was performed according to the same procedure as Experiment 1. Thus obtained $IC_{50}$ values [$\mu g/m\ell$] are represented in the following Table 4.

Table 4.

| Cancer Cell | Imatinib mesylate | Example 2 | Example 4 | Example 10 |
|---|---|---|---|---|
| A549 | 37.18 | 27.6 | 46.6 | 3.50 |
| KATO III | 32.58 | 30.04 | 32.35 | 3.26 |
| KB | 47.54 | 31.59 | 35.04 | 8.99 |
| HL60 | 35.68 | 17.74 | 27.79 | 4.28 |
| SK-OV-03 | >50.0 | 37.99 | >50.0 | 25.50 |
| MCF-7 | >50.0 | 36.22 | >50.0 | 6.96 |
| DU-145 | 9.04 | 30.33 | 41.26 | 5.51 |
| KG-1 | 31.22 | 7.31 | >50.0 | 3.31 |
| RPMI-6666 | 33.76 | 14.72 | 33.80 | 2.12 |
| SNU-182 | 44.00 | 24.72 | 48.04 | 7.94 |

As can be seen in the above Table 4, the compound of Example 2 according to the present invention showed $IC_{50}$ values of 1/4 time and 1/2 time or less than those of Imatinib mesylate against KG-1 and RPMI-6666, respectively. Further, the compound of Example 10 showed an improved activity than Imatimib mesylate against all the cells of A549, KATO III, HL60, SK-OV-03, MCF-7, DU-145, KG-1, RPMI-6666, and SNU-182. Particularly, it showed an activity of 15 times or more against RPMI-6666 at the same concentration.

Summarizing Tables 1 to 4, the compound of Example 4 showed an activity of 5 times or more against the CML cell line, K562, than the standard drug of Imatinib mesylate, and also showed a similarly excellent effect against the other cell lines, and so it is expected to be a drug that has a similar type but a far superior effect to Imatinib mesylate. The compound of Example 42 is also expected to have a better effect than that of Imatinib mesylate. Most example compounds according to the present invention represented a superior activity against U937 and L1210 to Imatinib mesylate, and particularly, the compounds of Examples 2 and 4 showed a far superior effect against U937, and the compounds of Examples 12 and 6 against L1210. Therefore, it is considered that a new therapeutic agent may be developed against these cancers.

On the other hand, the compounds of Examples 2 and 10 exhibited a far superior activity to Imatinib mesylate against the other cancer cells except K562. Particularly, since the compounds of Examples 2 and 10 showed a high activity against Acute Myelogenous Leukemia cell of KG-1 and Lymphoma cell of RPMI-6666, respectively, they are expected to be developed as new therapeutic agents against the other cancers besides the CML.

Experiment 5

Comparative pharmacokinetic test in white rats

On the previous day to the test, white rats (250~280g) were put under anesthesia by pentobarbital sodium (50mg/kg, I.P.). Then, cannula (polyethylene tube; diameter: 0.58mm) was introduced into the rats via the carotid artery, and drawn out to the back. After the operation, the rats were fasted for 16 hours and used for the test. Imatinib mesylate and the compound of Example 4 were orally administered in a dosage of 100㎎/kg, and blood was collected in 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours. The samples for HPLC analysis were prepared using the collected blood according to the following procedure and were analyzed under the following conditions.

Preparation of the samples for HPLC analysis

Blood was collected by an amount of 0.5㎖ at the prearranged time and centrifuged at 15000rpm for 7 minutes to separate 200㎕ of plasma. In order to remove proteins, MeOH was added in an amount of 400㎕, twice as much as the amount of plasma, and the mixture was shaken for 30 minutes. The mixture was centrifuged again at 15000rpm for 5 minutes to give 600㎕ of protein free supernatant, which is then analyzed by HPLC.

HPLC analysis conditions

Flow rate: 1.0 ㎖/min, UV detection at 267 nm

Column: 4.6 x 150 mm, 5C18-AR-II, COSMOSIL

Eluent: Mixture of ion pair sample (420㎖) and MeOH (580㎖)

Ion pair sample: 7.5g of 1-octanesulfonic acid was dissolved in about 800㎖ of water. The resulting mixture was adjusted to pH 2.5 using phosphoric acid and diluted with water to 1000㎖ volume.

When Imatinib mesylate and the compound of Example 4 were administered per oral to the white rats in a dosage of 100mg/kg, it was confirmed that Cmax (maximum blood concentration) and AUC (area under the curve of time-blood concentration) of the compound of Example 4 were about twice as much as those of Imatinib mesylate. Accordingly, pharmacokinetic test was carried out by orally administering the compound of Example 4 in a dosage of 50mg/kg, half of the above dosage, carrying out the test according to the same procedure as above, and comparing the result with that of Imatinib mesylate which was administered orally in a dosage of 100mg/kg. Here, the pharmacokinetic parameters are Tmax (time to reach the maximum blood concentration), Cmax (maximum blood concentration), AUC (area under the curve of time-blood concentration), and $T_{1/2}$ (half time in blood), and the AUC was calculated under trapezoid rule (see Table 5 and Figure 1).

Table 5.

| | Imatinib mesylate (100mg/kg) | Compound of Ex. 2 (50mg/kg) | Compound of Ex. 4 (50mg/kg) | Compound of Ex. 10 (50mg/kg) |
|---|---|---|---|---|
| Tmax (hr) | 2.3 | 1.5 | 2 | 1.5 |
| Cmax (μg/mℓ) | 2.724 | 2.197 | 3.155 | 1.358 |
| AUC | 26.461 | 26.181 | 22.951 | 12.056 |

As shown in the above Table 5, although the concentration of administration of Examples 2 and 4 is half of that of Imatinib mesylate, it was identified that their pharmacokinetic parameters of Tmax, Cmax, and AUC are similar to those of Imatinib mesylate with no statistical significance. However, the compound of Example 10 showed pharmacokinetic characteristics of about half as high as those of Imatinib mesylate and the compounds of Examples 2 and 4 at a dosage of 50mg/kg. On the basis of these results, it may be concluded that the compounds of Examples 2 and 4 exhibit the same effect as Imatinib mesylate when they are clinically applied at a daily dosage lower than that of Imatinib mesylate. Therefore, the compound of the present invention has a superior therapeutic effect and advantages in cost, etc., and also can be formulated into an oral dosage form (tablet or capsule) when industrially manufactured.

Experiment 6

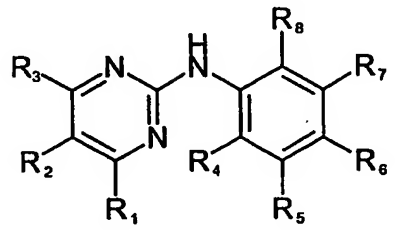
Acute toxicity test in mice

In order to determine the acute toxicity of the compound of the present invention, mice (24~26g) were fasted for 16 hours. One group consists of 10 males and 10 females. The first group is a control group and physiological saline was administered per oral to this group. The compounds of Examples 2, 4 and 10 were orally administered in a dosage of 2000mg/kg, the maximum dosage in acute toxicity test, to each test group. After the administration, clinical conditions of the mice were observed for 14 days and weight change was also measured. On the last day of the test, 14$^{th}$ day from the start, the mice were subjected to an autopsy in order to examine changes of the internal organs. During

the period of observation, neither abnormal response nor specific autopsy result was observed. Also, the body weight of the test groups does not show any change with statistical significance when compared with the control group. Further, since no mouse died during the test period, it was confirmed that the compounds of Examples 2, 4 and 10 have LD50 of 2,000mg/kg or more. This means that the compounds of the present invention including those of Examples 2, 4 and 10 are safe in the aspect of acute toxicity.

## CLAIMS

1. N-phenyl-2-pyrimidine-amine derivative represented by the following formula (1):



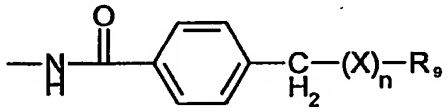
(1)

and its salt, in which

$R_1$ represents 3-pyridyl or 4-pyridyl,

$R_2$ and $R_3$ independently of one another represent hydrogen or lower alkyl,

$R_6$ or $R_7$ represents a radical having the following formula (2):



(2)

wherein X represents oxygen or NH, n=0 or 1, and $R_9$ represents aliphatic having at least 5 carbon atoms or heterocycle, or represents piperazinyl or homopiperazinyl each of which is substituted by lower alkyl, and

one or two among $R_4$, $R_5$, $R_7$, and $R_8$ when $R_6$ represents the radical of the above formula (2), or one or two among $R_4$, $R_5$, $R_6$, and $R_8$ when $R_7$ represents the radical of said formula (2) independently of one another represent halogen, lower alkyl, or lower alkoxy,

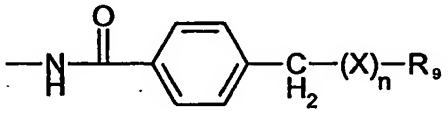
provided that $R_6$ or $R_7$ represents a radical of formula (2) wherein n=0 and $R_9$ is 4-methylpiperazine, then one or more of $R_4$, $R_5$, $R_7$, and $R_8$, or one or more of $R_4$, $R_5$, $R_6$, and $R_8$ are halogen.

2. The compound of claim 1 wherein

$R_1$ represents 3-pyridyl,

$R_2$ and $R_3$ independently of one another represent hydrogen,

$R_6$ or $R_7$ represents a radical having the following formula (2):



(2)

wherein X represents NH, n=0 or 1, and $R_9$ represents piperidine, 4-methylhomopiperazine, or 4-methylpiperazine, and

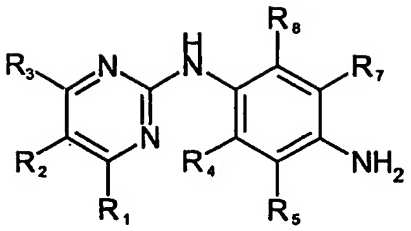
one or two among $R_4$, $R_5$, $R_7$, and $R_8$ when $R_6$ represents the radical of said formula (2), or one or two among $R_4$, $R_5$, $R_6$, and $R_8$ when $R_7$ represents the radical of the above formula (2) independently of one another represent fluoro, methyl, or methoxy.

3. The compound of claim 1 wherein $R_1$ represents 3-pyridyl, $R_2$, $R_3$, $R_4$, $R_5$, $R_7$, and $R_8$ independently of one another represent hydrogen, and $R_6$ represents the radical of formula (2) wherein n=0 and $R_9$ represents 4-methylhomopiperazine, or n=1, X represents NH, and $R_9$ represents 4-methylpiperazine.

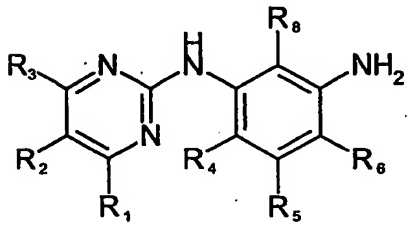
4. The compound of claim 1 wherein $R_1$ represents 3-pyridyl, $R_2$ and $R_3$, independently of one another represent hydrogen, $R_4$ represents methyl, $R_5$, $R_6$ and $R_8$ independently of one another represent hydrogen, and $R_7$ represents the radical of formula (2) wherein n=1, X represents NH, and $R_9$ represents 4-methylpiperazine.

5. A process for preparing the compound of formula (1) as defined in claim 1, which comprises reacting a compound represented by the following formula (3a) or (3b):

50

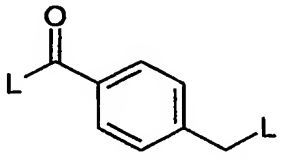


(3a)



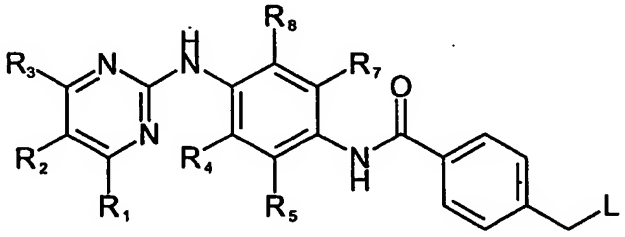
(3b)

wherein $R_1$ to $R_8$ are as defined in claim 1, with a compound represented by the following formula (4):

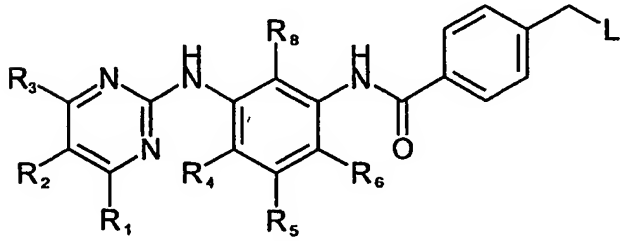


(4)

wherein L represents a leaving group, to produce a compound represented by the following formula (5a) or (5b):



(5a)



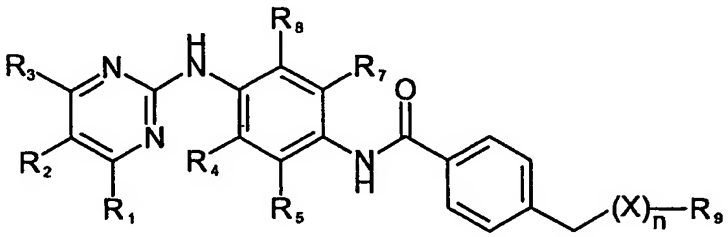
(5b)

wherein $R_1$ to $R_8$ and L are as defined above, and reacting the compound of

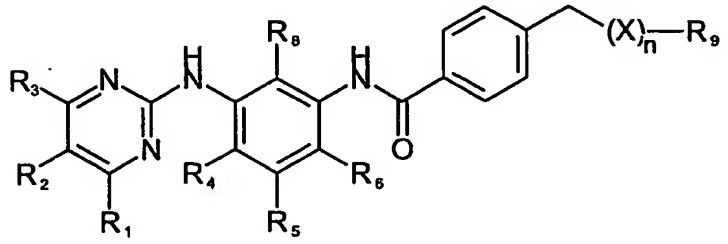
formula (5a) or (5b) with a compound represented by the following formula (6):

$$H(X)_n—R_9 \quad (6)$$

wherein X, n, and $R_9$ are as defined in claim 1, to give a compound represented by the following formula (1a) or (1b):



(1a)



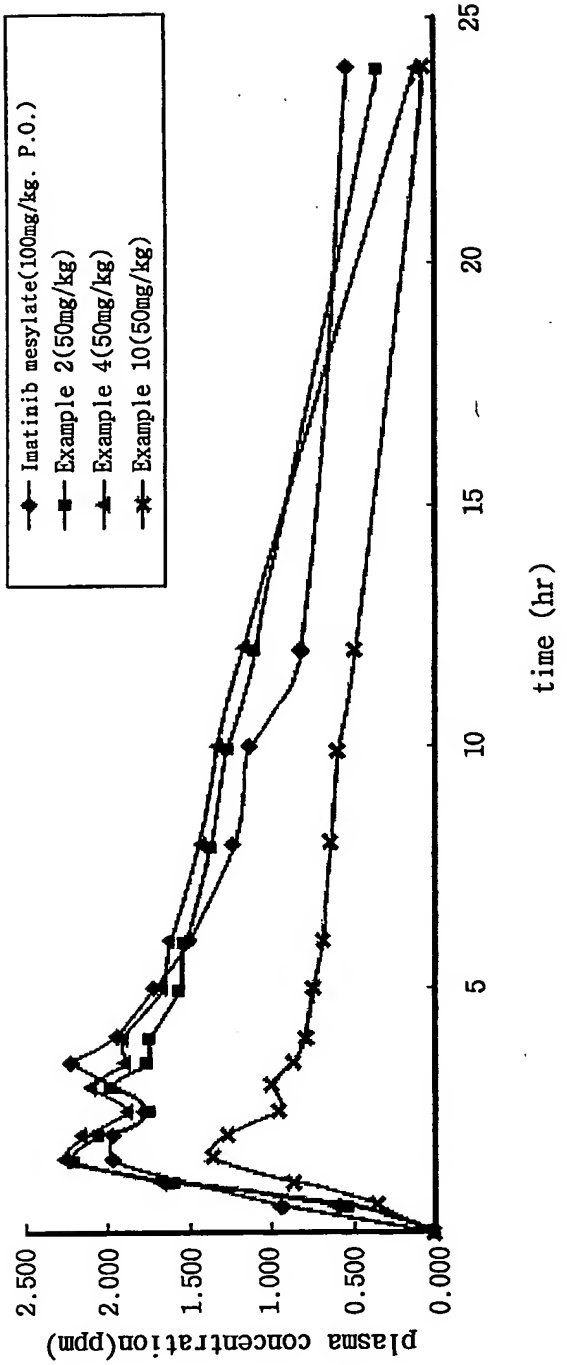
(1b)

wherein $R_1$ to $R_8$, X, n, and $R_9$ are as defined above.

6. A pharmaceutical composition for the prevention and treatment of tumor, lung cancer, or gastric cancer, which comprises the compound of formula (1) or its salt as defined in claim 1 as an active ingredient together with pharmaceutically acceptable carriers.

7. The composition of claim 6 which is used orally.

FIG. 1


Imatinib mesylate(100mg/kg. P.O.)
Example 2(50mg/kg)
Example 4(50mg/kg)
Example 10(50mg/kg)
plasma concentration(ppm)
2.500
2.000
1.500
1.000
0.500
0.000
time (hr)
5
10
15
20
25

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2003/001029

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC7 C07D 401/14

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D 401/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN[CASLINK, N-phenyl-2-pyrimidine-amine AND (anticancer OR antitumor)]
Pubmed [N-phenyl-2-pyrimidine-amine AND (anticancer OR antitumor)]

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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| X | WO 02/080925 A1 (NOVARTIS AG) 17 October 2002<br>See claim 1 | 1 - 4 |
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Information on patent family members

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